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Original article

Nutritional status of children and adolescents with cancer in Scotland: A prospective cohort study

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SUMMARY

Background and aims: Malnutrition (under and overnutrition) in paediatric cancer patients during and after treatment increases short and long-term side-effects; however, factors contributing to malnutrition and patterns of change in nutritional status are still unclear. The aims were to investigate the prevalence of malnutrition, patterns of change in nutritional status and factors contributing to malnutrition in Scottish paediatric cancer patients.

Methods: A prospective cohort study of Scottish children aged <18 years, diagnosed with and treated for cancer between Aug 2010 and Jan 2014 was performed. Clinical and nutritional data were collected at defined periods up to 36 months. Measurements of weight and height/length and arm anthropometry (mid-upper arm circumference (MUAC) and triceps skin-fold thickness (TSF)) were collected. Body composition was estimated from arm anthropometry using Frisancho's references and bio-electrical impedance (BIA). Malnutrition was defined according to UK BMI curves; undernutrition (<2.3rd centile; −2 SD), overweight (≥85th < 95th centile; ≥+1.05 SD < 1.63 SD) and obese (≥95th centile; ≥1.63 SD). We performed descriptive statistics and multilevel analysis. $p < 0.05$ was considered statistically significant.

Results: Eighty-two patients [median (IQR) age 3.9 (1.9–8.8) years; 56% males] were recruited. At diagnosis, the prevalence of undernutrition was 13%, overweight 7% and obesity 15%. TSF identified the highest prevalence of undernutrition (15%) and the lowest of obesity (1%). BMI [$p < 0.001$; 95% CI (1.31 −3.47)] and FM (BIA) [$p < 0.05$; 95% CI (0.006–0.08)] significantly increased after 3 months of treatment, whilst FFM (BIA) [$p < 0.05$; 95% CI (−0.78 to (−0.01))] significantly decreased during the first three months and these patterns remained until the end of the study. High-treatment risk significantly contributed to undernutrition during the first three months of treatment [$p = 0.04$; 95% CI (−16.8 to (−0.4))] and solid tumours had the highest prevalence of undernutrition [BMI (17%)].

Conclusions: Arm anthropometry (or BIA) alongside appropriate nutritional treatment that targets undernutrition initially and overnutrition at later stages should be implemented in routine clinical practice of paediatric cancer patients.

1. Introduction

Cancer is the most common disease related cause of childhood death in the UK [1]. Nonetheless 5-year survival rates have doubled in the last 40 years reaching 82%; however, this varies depending on the type of cancer, which ranges from over 90% for standard risk leukaemia and solid tumours, such as retinoblastoma, to between

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40 and 50% for metastatic neuroblastoma [1]. This improvement is due to more advanced, targeted and intensive therapies, more sophisticated technology and the success of medical clinical trials in combination with a more holistic approach to patient care [2–4]. Consequently, attention is focused on reduction of treatment-related sequelae during and after therapy [5,6]. This includes malnutrition, which may affect tolerance of therapy, risk of comorbidities and survival [5].

At present, there is not a single "gold standard" method that best assesses nutritional status in ill children [5]. Furthermore, children with cancer experience oedema, changes in body composition and tumours can weigh up to 10% of total body weight [7,8]. Misclassification of nutritional status can occur if weight, height and BMI are used in isolation [7,8]. Measurements of arm anthropometry including mid-upper arm circumference (MUAC) and triceps skinfold thickness (TSF) [9,10] as well as bioelectrical impedance (BIA) [11] allow to estimate body composition [9,10]. Therefore, for a more comprehensive assessment a combination of anthropometry and body composition methods have been recommended [6].

Malnutrition is defined as undernutrition, overnutrition and/or poor growth [12,13] and protein energy malnutrition (PEM) as reduced fat free mass (FFM), with either low fat mass (FM) (undernutrition), healthy FM (well-nourished) or high FM (overnutrition) [14–16]. Malnutrition in paediatric cancer patients has long been recognised [17–22], yet its management remains variable [5,19], there are differences in reported prevalence and its associations with clinical outcomes are still unclear, particularly for overnutrition [6]. Furthermore, most research has focused on undernutrition with overnutrition during cancer treatment being largely overlooked [6]. The prevalence of undernutrition ranges between 0 and 65% worldwide and between 4 and 15% in developed countries. This is highest in children diagnosed with solid tumours, which ranges from 23.5 to 50% at diagnosis to 20–46% in survivorship; whereas, children diagnosed with haematological malignancies, mainly Acute Lymphoblastic Leukaemia (ALL), have the lowest prevalence of undernutrition at all stages (9.5–14%) [6]. Finally, data reporting overnutrition (overweight and obesity) is scarce, but is more consistent with the methods used to diagnose it (BMI), and has focused mainly on children diagnosed with haematological malignancies [6]. Nonetheless, the number of cases of overnutrition increases from 15% at diagnosis to 38% at the end of therapy and is most prevalent in children diagnosed with brain tumours (50%), followed by haematological malignancies (15–40%) and solid tumours (21–35%) [6].

At present, most studies are of retrospective or cross-sectional nature [6]. The few population based prospective cohort studies published have focused mainly on children diagnosed with haematological malignancies and most do not report nutritional status at all stages of treatment [6]. Furthermore, a recent systematic review [6] emphasised the need to identify when changes in nutritional status occur and using different forms of measurements in children with cancer for performing population based longitudinal cohort studies. To date, only one small preliminary study of this nature has been published in Scotland [23] and one in the Netherlands [19]. In light of this, our aims were: (i) to investigate the prevalence of malnutrition in newly diagnosed paediatric cancer patients and during the study period at defined time points for 36 months; (ii) to identify changes in anthropometry and body composition during this period; (iii) to determine both potential factors contributing to malnutrition and (iv) whether nutritional status (BMI centile) is associated with clinical outcomes.

2. Materials and methods

2.1. Study design, population and time-line

A prospective cohort study was performed. Eligibility criteria included: children aged <18 years; diagnosed with cancer (ICCC-3) [24] or Langerhans Cell Histiocytosis between Aug-2010 and Feb-2014; attending the South East Scotland regional centre for Haematology and Oncology at the Royal Hospital for Sick Children (RHSC), Edinburgh or Ninewells Hospital, Dundee and patients were recruited consecutively. We excluded children who were treated with palliative intent. Children were recruited continuously during the study period and were monitored for a maximum period of 36 months and a minimum of 3 months. Measurements were obtained at baseline, 3, 6, 9 and 12 months and every 6 months thereafter by two trained researchers in clinic or on the ward.

Anonymised control data were obtained from medical records of patients who met the eligibility criteria but did not consent to the study. This was done to establish whether the cohort was representative of the SE Scottish paediatric oncology population.

2.2. Demographics and clinical parameters

Clinical data (diagnosis, treatment protocol and length of treatment) and demographic data (age, gender, ethnicity and socioeconomic deprivation) were collected from medical notes. Clinical outcome was classified as "event free survival" or "event" (relapse, death, new metastasis or becoming palliative during the study period). Treatment intensity was classified low, medium and high according to Kazak et al. [25]. As a proxy marker for socioeconomic deprivation of individuals, we used the Standard Index of Multiple Deprivation (SIMD) [26]. The paediatric cancer cohort was grouped according to the wider definition of solid tumours, haematological cancers, brain tumours and other associated diagnoses.

Ethical approval was granted from NHS Scotland (NHS REC 06-51104-52).

2.3. Measurements of nutritional status and reference values

Measurements of weight and height at the time of diagnosis (prior to recruitment) were obtained from clinical notes. Following recruitment, all measurements were taken at each follow up. Measurements of growth and body composition were repeated three times. Weight and height (or length for infants <2 years) were obtained following standard procedures [27]. BMI was calculated and centiles were obtained from LMS Growth programme [28]. Nutritional status was classified as underweight (BMI $\leq$ 2.3rd centile; -2 SD), healthy weight (BMI > 2.3rd to <85th centile; $>-2 < +2$ SD), overweight (BMI $\geq$ 85th ($\geq+1.05$ SD) and <95th (<1.63 SD) centile) and obese ($\geq$95th centile ($\geq$1.63 SD)) [28,29].

Arm anthropometry [Mid-upper arm circumference (MUAC) and triceps-skinfold thickness (TSF)] was measured using standard techniques (Harpended Skinfold caliper) [10]. Data were expressed as centiles using Frisancho reference values [10,30]. The crude measures of TSF (mm) and MUAC (mm) were used to calculate upper arm muscle area (UAMA) and upper arm fat area (UAFA) using the Frisancho equation and centiles [9]. All references were adjusted for age and gender and definitions of malnutrition (MUAC, TSF, UAMA and UAFA) were: undernutrition $\leq$ 5th centile [8,10,31], overnutrition $\geq$ 85th to <95th centile and obesity $\geq$ 95th centile [9,10]. Protein energy malnutrition was defined as UAMA $\leq$ 5th centile [10] with/without high fat mass (BMI $\geq$ 85th centile) in children older 1 year old as per reference [9,32,33]. The prevalence of undernutrition was established using BMI, MUAC and TSF and

overweight and obesity using BMI and TSF. Categorical data (centiles categories) were normalised by calculating the percentage of the 50th centile.

The percentage of fat mass (FM) and fat free mass (FFM) was measured using a calibrated SF-BIA Quantum II RJL System (frequency 50 kHz) following manufacturer's instructions. The estimation of FM and FFM was calculated using Schaefer et al. [34,35] total body water equation and the reference values used were Fomon et al. [36,37] for children < 10 years old and Wells et al. [37] for children aged 10–18 years.

The intra and inter-observer technical error of measurement (TEM) for skin folds and arm circumferences were calculated and expressed as cm and percentages. All were below the proposed accreditation for level 2 post-course anthropometrists [38]; MUAC (intra TEM cm (%) observer 1 = 0.12 (0.6%); observer 2 = 0.11 (0.3%); inter TEM 2.78 (1.70)%) and TSF (intra TEM observer 1 = 0.17 (1.3%); observer 2 = 0.13 (1.23%); inter TEM 2.83 (1.69%)).

2.4. Dietary intake and nutritional treatment

Total energy intake (TEI) was assessed using a 24 h multi-pass recall method [39] to establish patterns of change throughout the study period. This was analysed in WinDiets® (Univation Ltd 2005) programme [40]. Nutritional treatment was prescribed according to Subjective Global assessment by the multidisciplinary team and consisted of enteral ± parenteral nutrition. Estimated total energy requirements (TER) were calculated using the Henry equation [41] and a low physical activity level (PAL) of 10th centile [19,42]. TEI and estimated TER were compared. Data were then normalised by calculating the percentage of TEI from the TER.

2.5. Statistical analyses

The Statistical Package for Social Science (IBM-SPSS for Windows Statistics, version 19) was employed to analyse all data. Parametric test and mean (±SD) were used for normally distributed data and non-parametric tests and median (IQR) for non-normally distributed data. The agreement between FM% obtained from arm anthropometry and SF-BIA was calculated to account for discrepancies between these two methods. Descriptive statistics were used to evaluate the prevalence of malnutrition and changes in growth and body composition at defined time points for 36 months (aim i); To establish patterns of change in growth (BMI and HFA centiles) and body composition (FFM and FM established by arm anthropometry and BIA) over time a multilevel growth model was used (aim ii). All diagnostic criteria were analysed altogether ($p > 0.05$). Changes in growth and body composition have been presented at 0–3, 0–9 and 0–18 time intervals due to the statistically significant differences found in the variables' trajectories at these time points. To establish factors that may contribute to changes in nutritional status, established using BMI centile (primary outcome), at each time point (0–3 months, 0–9 months and 0–18 months) the mixed multilevel model was used (aim iii). The following factors were tested: diagnostic criteria, treatment risk, age at diagnosis, nutritional treatment and TEI. Factors were tested one at the time and only those that reached a relaxed significance of 0.1 were included in the conditional model. No multilevel analysis was performed after 18 months due to the reduced sample size. Univariate associations between demographic, clinical and nutritional data and clinical outcomes (event free survival or event) were established by χ^2-test (aim iv). Results were expressed as 95% CI and odds ratios. $p < 0.05$ was considered statistically significant.

We followed the STROBE guidelines for the presentation of our data [43].

3. Results

3.1. Demographic and clinical characteristics

179 patients were diagnosed with paediatric cancer between Aug 2010 and Feb 2014. Of these 78 (43%) were excluded (Fig. 1) and 101 (57%) were considered eligible. 82 (81%) were recruited, whilst 19 (19%) refused to participate mainly due to stress. Demographic and clinical characteristics of the population are presented in Table 1 and the patient's accrual (Fig. 1) and follow up (Fig. 2). There were no statistically significant differences between the paediatric cancer cohort and the paediatric cancer controls (refusals). BMI centiles of males and females from our paediatric cancer cohort did not differed at any time point. Twenty-four treatment protocols were used to treat the paediatric cancer cohort, the median time follow-up was 312 (IQR 123.5–653.2) days and the time between diagnosis and baseline measurements was 15.5 (IQR 10.0–25.0) days and between the start of cancer treatment and baseline measurements was 9.5 (IQR 6.0–19.5) days. All patients were receiving cancer treatment when the measurements were taken at baseline.

At the end of the study (May 2014), the survival rate was 90% (74), the death rate was 10% (8) and the event free survival rate was 85% (70). Thus 15% (12) of patients had “events” (relapse, cancer metastasis or did not respond to treatment). Of these, 67% (8/12) died, 17% (2/12) continued treatment with palliative intent, 17% (2/12) were receiving second-line treatment by the end of the study, of whom 8% (1/12) survived.

55 (67%) patients were referred to the Dietitian for nutritional assessment during the study. The reasons for referral were: undernutrition/weight loss (16/55; 25%), reduced oral intake (10/55; 18%), temporary gut failure (10/55; 18%), to prevent weight loss (7/55; 13%), dysphagia (4/55; 7%), steroid induced diabetes (2/55; 4%), mucositis (1/55; 2%) and following parent's request (1/55; 2%). Of these, 50 (61%) were prescribed some form of nutritional support and 5 (6%) had general dietary advice. In total, 14/50 (28%) patients received oral nutritional support (ONS), 17/50 (34%) naso-gastric tube feeding (NG), 4/50 (8%) percutaneous endoscopic gastrostomy feeding (PEG), 1/50 (2%) total parenteral nutrition (TPN) and 15/50 (30%) advanced nutritional support (NS/PEG and TPN).

Mean percentage TEI of individual TER (TEI% of TER) throughout the study period was 161% (±42%) and this was consistently higher than TER at all stages apart from the 3 months follow up, which was lower [82% (±51%)]. TEI% of TER ranged between 155% (±78%) at baseline to 182% (±84%) at 9 months and patients on nutritional support (152% ± 14%) had similar TEI% of TER than patients who were not (157% ± 17%) throughout the study period ($p = 0.4$; 95% CI −168 to 60). FM% obtained from arm anthropometry and SF-BIA had a mean difference of 0.09% (95% CI −1.0 to 1.2).

3.2. Prevalence of malnutrition

The prevalence of malnutrition (undernutrition, overweight and obesity) varied at each time point and with each measurement (Fig. 2). Undernutrition was highest at diagnosis and baseline than at any other time during the study period. At this stage, it ranged between 13% [BMI (11/81) and MUAC (10/79)] and 15% [TSF (11/75)]. According to BMI, there were no undernourished patients at 9, 12 and 18 months; however, MUAC and TSF identified between 3 and 6% at these time points. No patient was undernourished at the end of the study period (30 and 36 months). Overweight ranged between 7 and 21% during the study period and both BMI and TSF identified similar prevalence at baseline, 3, 6, 18 and 24 months; however, this differed from each other at 9 and 12 months with differences of 7% and 21% respectively. Overweight was highest at

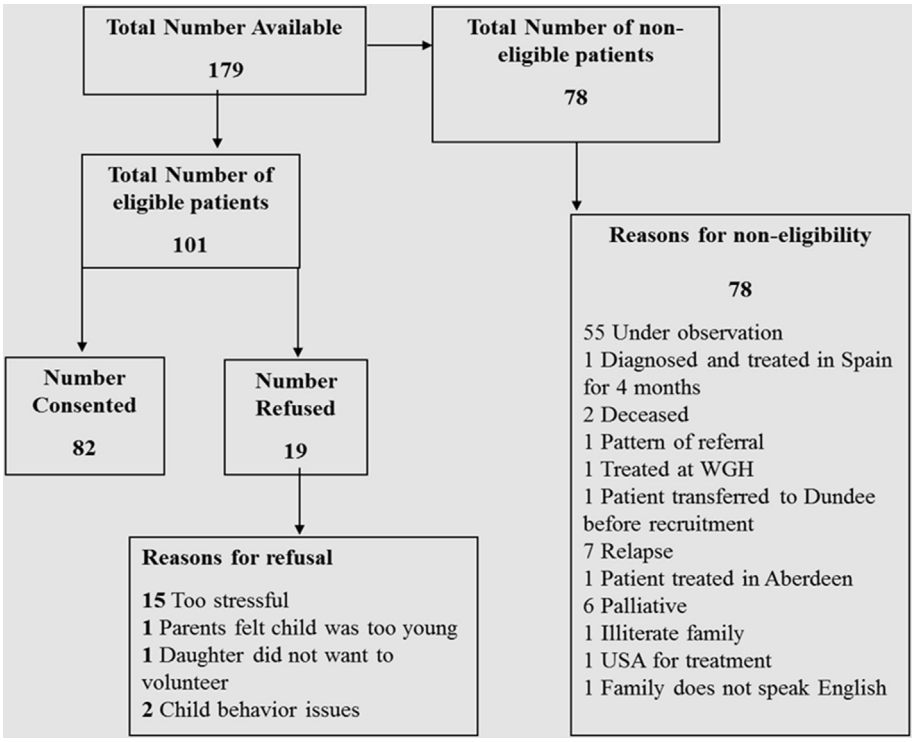

Fig. 1. Flow diagram showing patient's accrual.

30 [BMI and TSF; 2/12 (17%)] and 36 months [TSF; 2/7 (29%)]. Finally, BMI identified consistently higher prevalence of obesity than TSF throughout the study period and there were no obese patients at 36 months. Obesity was least prevalent at diagnosis [BMI; 12/82 (15%) and TSF; 1/75 (1%)] and most prevalent at 30 months [BMI; 4/12 (33%) and TSF; 3/12 (25%)].

Table 2 shows that children diagnosed with solid tumours had the highest prevalence of undernutrition. In contrast, patients with brain tumours and other associated diagnoses had the highest prevalence of overweight and obesity.

PEM (established using UAMA) was prevalent in all paediatric cancer diagnoses during the first 24 months of the study (Fig. 3 left), particularly at 3 (6/62, 10%) and 24 months (3/24, 12.5%), whilst no patient was classified as PEM at either 30 or 36 months. Fig. 3 right shows the prevalence of malnutrition identified by UAFA in all paediatric cancer patients. Undernutrition was highest at baseline (9/64, 14%) and decreased over time, whereas the number of both overweight and obesity patients increased from 4% (3/64) at baseline to 8% (1/12) overweight and 25% (3/12) obese patients. Furthermore, UAMA and BMI did not classify patients in the same nutritional status category between 3 months and 24 months of the study and a considerable number of PEM (UAMA) patients were also classified by BMI as well-nourished, overweight and one obese (Table 3).

3.3. Patterns of change in anthropometry and body composition

Fig. 4 shows changes in median (IQR) BMI (4 left) and HFA (4 right) centiles. BMI of paediatric cancer patients increased steadily from the time of diagnosis [48 (19.0–84.5)] until the 30 month time point [85 (39–98)]. Children diagnosed with solid tumours had consistently lower BMI centiles than the other diagnostic criteria; however this was not statistically significantly different ($p < 0.05$). HFA of all paediatric cancer patients was above the 50th centile [55 (26.5–74.0)] at diagnosis and this decreased at every stage until it reached a nadir at 6 months [41 (23.0–64.0)]. From this point, HFA increased steadily until it reached a peak at 30 months [69.5 (47.7–93.7)]. Children diagnosed with solid tumours had the highest HFA at the time of diagnosis [62 (25–76)] and baseline [62.5 (35.5–79.7)], whilst those diagnosed with haematological malignancies had the lowest HFA centiles at baseline [36 (17.5–36.0)]. This group remained with the lowest HFA centiles for 24 months, at which point it increased considerably reaching the 70th centile (IQR 32–86.9) and levelling with the other cancer groups.

Fig. 5(a and b) illustrates that MUAC and UAMA both remained consistent; however, FFM% estimated from both arm anthropometry and BIA decreased marginally during the study (Fig. 5c). In contrast, TSF, UAFA and FM% (estimated from arm anthropometry and BIA) all increased during this time (Fig. 5 a, b and d).

Multilevel growth model (Table 4) showed a statistically significant increase in mean BMI centile from 0 to 3 months (1.5th centile; 95% CI 1.31–3.47; $p < 0.001$) and from 0 to 18 months (19.0th centile; 95% CI 1.31–3.47; $p < 0.001$). There were no statistically significant changes in mean HFA centile at any time interval. There were not statistical significant changes in either FFM or FM established using arm anthropometry, apart from the 0–3 months' time interval where there was a significant reduction in the percentage of FFM (−0.9%; 95% CI −1.6 to −0.5; $p < 0.01$). In contrast, the percentage of FFM established using a BIA decreased significantly between 0 and 3 months (−1.71%; 95% CI −0.78 to −0.01; $p < 0.05$) and 0–9 months (−2.83%; 95% CI −0.13 to −0.01; $p < 0.02$).

3.4. Factors contributing to changes in nutritional status (BMI centile)

Factors contributing to changes in BMI centile between 0 and 3 months (intercept: estimate 48.4; df 79; 95% CI 41–55; $p < 0.001$), 0–9 months (estimate 44.13; df 296; 95% CI

Table 1
Characteristics of the $n = 82$ Paediatric Oncology cohort and $n = 22$[a] controls (non-participants).

Patients' characteristics	Cohort			Controls			p
	Median	IQR	95% CI	Median	IQR	95% CI	
Age at diagnosis (years)	3.88	1.96–8.83	4.69–6.88	6.52	3.91–10.65	5.37–9.26	0.06[c]
BMI centile	44.00	12.50–80.50	27.90–65.41	45.00	4.90–70.00	20.01–54.98	0.2[c]
	N		%	*N*		%	
Gender							0.5[d]
Male	46		56	10		45.5	
Female	36		44	12		54.5	
Diagnostic criteria							0.9[e]
Solid tumours	39		47	10		45.5	
Haematological malignancies	36		43	11		50	
Brain tumours	7		8.5	1		4.5	
Other associated diagnosis	4		5	0		5	
Diagnosis ICCC-3							
I – Leukaemias	35		43	11		50	
ALL	29		35	11		50	
AML	3		4	0		0	
CML	2		2	0		0	
HLH	1		1	0		0	
II – Lymphoma	10		12	3		14	
III – CNS tumour	5		6	2		9	
IV – Neuroblastoma	6		7	2		9	
V – Retinoblastoma	2		2	0		0	
VI – Renal tumour	6		7	0		0	
VII – Hepatic tumours	1		1	0		0	
VIII – Malignant bone tumours	4		5	3		14	
IX – Soft tissue sarcoma	5		6	1		4	
X – Germ cell tumours	1		1	0		0	
XI – Malignant epithelial neoplasm	4		5	0		0	
XII – Others and unspecified malignant neoplasms	0		0	0		0	
Other associated diagnosis	3		4	0		0	
LCH	3		4	0		0	
Intensity of treatment							0.9[d]
Low	18		22	4		18	
Medium	30		37	8		36	
High	34		41	10		46	
Socioeconomic status[b]							0.6[d]
I	15		18	7		32	
II	12		15	2		9	
III	15		18	2		9	
IV	24		29	8		36	
V	15		18	3		14	
Ethnicity							0.5[e]
White	80		98	21		95.5	
Non-white	2		2.4	1		4.5	

LCH: Langerham's cell histiocytosis.
[a] $N = 22$: 19 (refused to participate) + 3 (met criteria but were not approached as advised by consultants).
[b] Socio-economic status (SES) I–V where I denotes the most deprived and V the economically most advantageous families.
[c] Mann–Whitney.
[d] Chi square test.
[e] Fisher's exact test.

32.3–55.9; $p < 0.001$) or 0–18 months (estimate 72; df 284; 95% CI 34.7–109.5; $p < 0.01$) were tested in the fixed model. Between 0 and 3 months, diagnostic criteria (estimate 8.1; df 75; 95% CI −0.41 to −1.1; $p < 0.04$), treatment risk (estimate −16.5; df 75; 95% CI −24.3 to −8.6; $p < 0.001$) and TEI (estimate 0.02; df 51; 95% CI 0.002–0.2; $p = 0.02$) all contributed to changes in BMI centile. Both diagnostic criteria (solid tumours) and high treatment risk contributed to a decreased in BMI centile, whereby TEI contributed to an increased in BMI centile during this period. No single factor contributed to changes in BMI centile between 0 and 9 months or 0–18 months; however, nutritional support (estimate 14.3; df 32; 95% CI −2.3 to 31; $p = 0.09$) was further tested in the conditional model (relaxed p value of 0.1) between 0 and 18 months. The conditional model showed that only high treatment risk contributed to a decreased in BMI centile (estimate −8.6; df 67; 95% CI −16.8 to −4.0; $p = 0.04$) during the first 3 months of treatment (Fig. S1).

3.5. Associations between nutritional status at diagnosis and clinical outcome

Only undernutrition (<2.3rd centile) at diagnosis was statistically significantly associated with "event" (relapse, death or becoming palliative) [Fisher's Exact test (19.901; $p < 0.001$)]. Furthermore, patients who were undernourished at diagnosis were 14 times more likely to have an event (RR = 14). Of these 67% (7/11) were treated with a high treatment intensity protocol and 17% (4/11) with either medium or low treatment intensity protocols. Overnutrition (overweight and obesity) at diagnosis was not statistically significantly associated with event [Fisher Exact test (7.10; $p = 0.3$)]

4. Discussion

This is the first prospective cohort study investigating the prevalence of malnutrition, patterns of change in nutritional status and

Time point	Patients availability	Drop outs*	BMI	MUAC	TSF	BIA	Dietary intake
Recruitment	82	0	81	79	75	60	77
3 months	82	6	75	71	70	56	75
6 months	73	19	54	49	49	38	54
9 months	65	14	51	48	47	37	51
12 months	55	14	42	41	40	30	42
18 months	47	13	34	33	32	28	34
24 months	35	11	24	24	24	20	24
30 months	19	7	12	12	12	10	12
36 months	16	9	7	7	7	6	7

Fig. 2. Patient's follow up at each time point and number of patients having had each type of measurement taken. *Drop outs due to: deceased patients, palliative treatment, treatment given in centres other than RHSC, Edinburgh and Ninewells Hospital, Dundee and patients who missed appointments.

Table 2
Prevalence of malnutrition according to BMI and TSF and stratified by type of cancer.

Time line	Nutritional status	Solid tumours				Haematological malignancies				Brain tumours				OAD[a]			
		BMI		TSF		BMI		TSF		BMI		TSF		BMI		TSF	
		%	N	%	N	%	N	%	N	%	N	%	N	%		%	N
Baseline	Undernutrition	17[b]	35	18	33	11[b]	36	12	33	14[b]	7	17	6	0	4	0	4
	Overweight	0		9		5.5		9		28.5		0		0		25	
	Obesity	8.5		0		14		0		28.5		17		50[b]		0	
3 Months	Undernutrition	12.5	32	3	31	3	35	6	32	0	5	0	5	0	3	25	3
	Overweight	3		13		14		9		60[b]		0		0		0	
	Obesity	5		3		14		6		20		20		33		0	
6 Months	Undernutrition	0	24	0	22	4	23	5	20	0	3	33[b]	3	0	4	0	4
	Overweight	8.3		9		17		25		33[b]		0		0		0	
	Obesity	8.3		13		26		15		33[b]		33[b]		25		0	
12 Months	Undernutrition	0	16	0	16	0	19	0	17	0	3	0	3	–	0	33[b]	3
	Overweight	6		19		42[b]		23.5		33[b]		33[b]		–		0	
	Obesity	0		0		21		23.5		0				–		0	
24 Months	Undernutrition	12.5[b]	8	0	7	0	14	0	14	–	0	–	0	–	0	–	0
	Overweight	0		14		14		7		–		–		–		–	
	Obesity	12.5		28.5		28.5		26		–		–		–		–	
30 Months	Undernutrition	0	5	0	5	0	6	0	6	0	1	0	1	–	0	–	0
	Overweight	0		0		33		33		0		0		–		–	
	Obesity	20		20		50		33		0		100		–		–	

[a] OAD: other associated diagnoses ($N = 4$; Langerham's cell histiocytosis).
[b] χ^2-test; $p < 0.05$ against undernutrition, overweight and obesity UK prevalence (DH 2012).

factors contributing to malnutrition during treatment in paediatric cancer patients from Scotland. Our results show that undernutrition was highest during the initial phases of treatment and no child was undernourished at the end. In contrast, overnutrition increased over time. Children diagnosed with solid tumours exhibited the highest prevalence of undernutrition; whereas, overnutrition was highest in brain tumours and in other associated diagnoses (LCH). Overall BMI and FM% (BIA) significantly increased at 3 and 18 months and at 3 and 9 months respectively; whilst FFM% (BIA) significantly decreased at 3 and 9 months. High treatment risk significantly contributed to undernutrition during the first 3 months of treatment and undernutrition at diagnosis was significantly associated with an event (relapse, becoming palliative or death).

4.1. Prevalence of malnutrition in paediatric cancer patients

Undernutrition ranged between 13 and 15% in newly diagnosed patients. This is in line with a recent a systematic review [6], but higher than that reported in the Netherlands (8%) [19]. Our results also showed that undernutrition decreased over time and that no patient was undernourished at the end of the study. This is consistent with findings from elsewhere [44], but contrast with a systematic review, which reported high prevalence of undernutrition (20%) at the end of treatment [6]. The higher prevalence of undernutrition at diagnosis is not surprising and likely to be multifactorial in origin. This can be the result of tumour burden (with the consequent increase in total energy expenditure

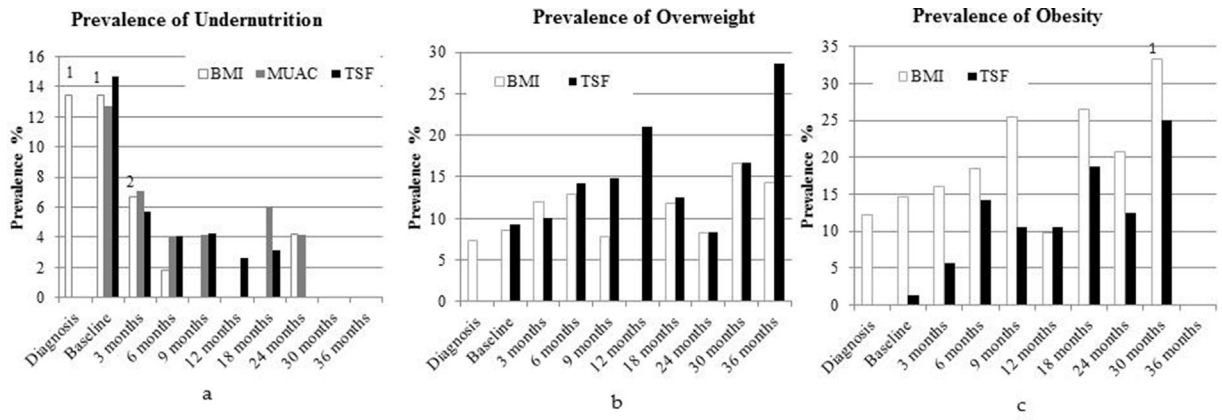

Fig. 3. Prevalence of malnutrition in paediatric cancer patients. Left. Prevalence of undernutrition according to BMI (<2.3rd centile), MUAC (<5th centile) and TSF (<5th centile) in all cancer diagnoses. $^{1}\chi^{2}$ (9.65), $p = 0.03$; $^{2}\chi^{2}$ (5.274), $p = 0.025$ against UK prevalence of undernutrition (DH 2012). For BMI, MUAC and TSF *n* values at different time points see Fig. 1. Centre. Prevalence of overweight according to BMI (≥85th centile ≤95th centile) and TSF (≥85th to ≤95th centile) in all cancer diagnoses. For BMI and TSF *n* values at different time points see Fig. 1. Right. Prevalence of Obesity at different stages of the disease and according to BMI (>95th centile) and TSF (>95th centile) in all cancers. $^{1}\chi^{2}$-test (5.274), $p = 0.03$ against UK prevalence of obesity (DH 2012). For BMI and TSF *n* values at different time points see Table 1.

Table 3
Comparison between children identified as PEM by UAMA and the nutritional status established by BMI.

Time line	UAMA	BMI			
	PEM < 5th C	Undernourished < 2.3rd C	Well-nourished > 2.3rd < 85th C	Overweight ≥ 85th < 95th C	Obese ≥ 95th C
Baseline	3	2	1		
3 Months	6	1	4		1
6 Months	4		4		
9 Months	3		2	1	
12 Months	3		3		
18 Months	1		1		
24 Months	3	1	1	1	

PEM: protein energy malnutrition; UAMA: upper arm muscle area.

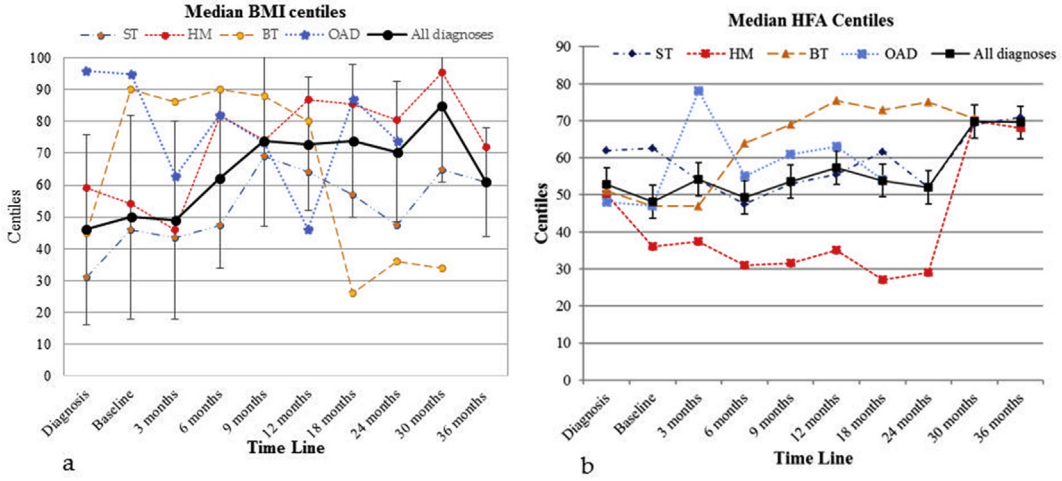

Fig. 4. Prevalence (expressed as a percentage) of protein energy malnutrition in paediatric cancer patients during the study period (left) and prevalence of malnutrition established using UAFA in all paediatric cancer patients at different stages of the disease (right). UAMA: upper arm muscle area; UAFA: upper are fat area.

associated with anorexia) [44] and treatment side-effects from the initial intensive therapy [18].

In contrast to the Netherlands [19] and data from a recent systematic review [6], but in agreement with findings from Canada [45,46] and Switzerland [47], our study showed a high prevalence of overweight (8–9%) and obesity (1–14%) in newly diagnosed patients, which increased further to 14–28% (overweight) and 25–33% (obesity) at later stages. The high prevalence of overnutrition at diagnosis may be a reflection of the high prevalence of obesity seen in Scottish children; however, overnutrition at later stages was higher in paediatric cancer patients than healthy British children [48]. Of note, the data from later stages should be interpreted with caution due to

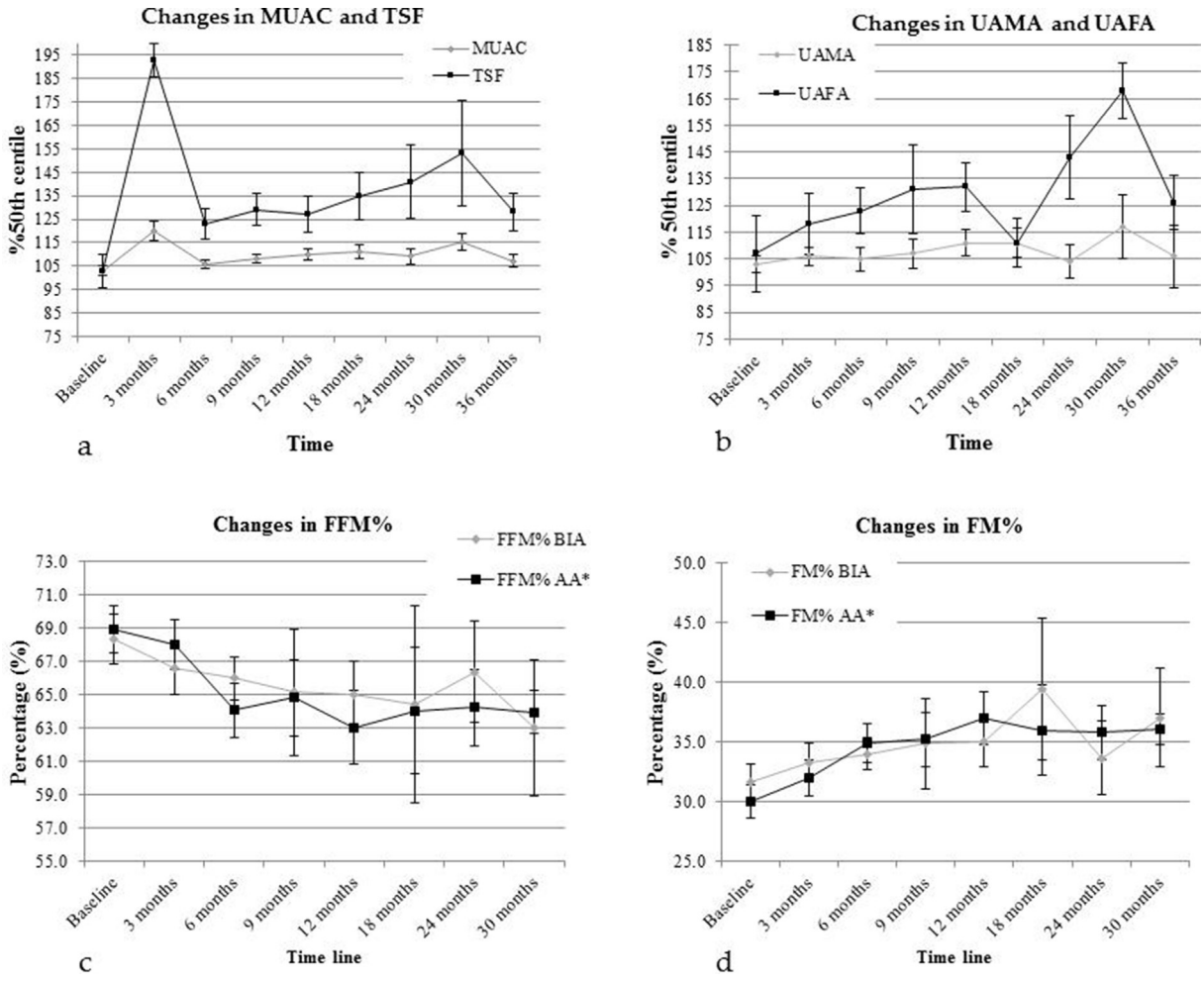

Fig. 5. Median BMI centiles (left) and Median Height for Age Centiles (right). Error bars are expressed as IQR.

the small sample size. Nonetheless, these findings are supported by others, especially in survivors of childhood cancer [49].

Stratification of the data by type of cancer revealed results consistent with most studies [6,19]. Children diagnosed with solid tumours (17–22%) exhibited the highest prevalence of undernutrition (17–22%) followed by brain tumours (9–17%) and haematological malignancies (3–12%) during the initial phases of treatment. In contrast, overweight and obesity were highest in OAD (LCH) (0–25% vs. 0–50%) and brain tumours (0–28.5% vs. 17–28.5%), also at the start of treatment. Comparison of these results with other studies is difficult due to the paucity of evidence looking at overnutrition in brain tumours and in children LCH [6]. Overweight and obesity increased during the course of treatment in all type of cancers, particularly in haematological malignancies and brain tumours. Therefore, our study suggests that current nutritional practices have become very successful at treating undernutrition; however, overnutrition has largely been overlooked and consequently left untreated. This may in part be attributed to current local nutrition policies, reduced number of specialist Oncologist/Haematologist Dietitians, who have to prioritise undernutrition, and the inexistence of specific clinical nutritional guidelines for the management of paediatric cancer.

4.2. Patterns of change in anthropometry and body composition

Analogous to findings from the Netherlands [19], our study showed that BMI and FM (measured with both arm anthropometry and BIA) increased significantly at 3 months. Interestingly, BMI had a second significant increment at 18 months, whilst FM attained significance at 9 months. In contrast, FFM declined significantly at 3 and 9 months when this was assessed using BIA. During this initial period of increase in BMI and FM, HFA centiles decreased significantly. Like Brinksma et al. [19], our study highlights that changes in anthropometry and body composition occur early on in paediatric cancer patients. Our study adds that both the increasing trend of BMI and FM and the reducing trend in FFM continued for 36 months and these changes persist into adulthood [50]. The consequences of reduced FFM during treatment include poor linear growth, loss of muscle strength, reduced tolerance of therapy and an increased in both treatment side-effects and infections risk [51]. Furthermore, the reduced FFM accompanied by high BMI and FM in survivorship increases cardiovascular risk profile in later life, more so than in the general population [2].

Current Scottish National Paediatric Oncology Dietetic Practices base their nutritional assessments on either weight for height or weight only. Although, rapid weight loss is an indicator for acute undernutrition, this measurement alone does not estimate body composition or PEM. Furthermore, the equations used in current paediatric oncology clinical practice to estimate TER take into consideration growth and a physical activity level (PAL) of 25th centile [41,48]. Our study, like others [6], has demonstrated that there is a stagnation of linear growth, especially in children diagnosed with haematological malignancies and during the first 3 months of treatment. Moreover, there is evidence of a sedentary

Table 4
Mean changes in nutritional status established in 3, 9 and 18 months intervals.

Growth	0–3 Months			0–9 Months			0–18 Months		
	Change	95% CI	*p* Value	Change	95% CI	*p* Value	Change	95% CI	*p* Value
BMI C	1.5	1.31–3.47	<0.001	15.9	−0.1 to 0.2	0.6	19	1.31–3.47	<0.001
HFA C	−1.3	−5.9 to 0.04	0.05	−3.9	−0.4 to 0.02	0.07	−4.2	−0.005 to 0.24	0.06
Body composition									
FFM% AA	−0.9%	−1.6 to (−0.5)	<0.001	−4.1%	−0.09 to 0.06	0.7	−4.87%	−0.01 to 0.02	0.7
FFM% BIA	−1.71%	−0.78 to (−0.01)	<0.05	−2.83%	−0.13 to (−0.01)	<0.02	−3.88%	−0.01 to 0.01	0.8
FM% AA	1.92%	−0.01 to 0.02	0.8	5.22%	−0.06 to 0.08	0.7	5.98%	−0.01 to 0.02	0.8
FM% BIA	1.71%	0.006–0.077	<0.05	3.1%	0.01–0.1	<0.02	3.9%	−0.01 to 0.01	0.4

lifestyle during and after treatment among patients [42]. These two factors might contribute to an overestimation of TER, which in turn may lead to overnutrition.

Consistent with a systematic review [6], we have clearly shown a discrepancy in identifying malnutrition between the different measurements. Arm anthropometry classified consistently more children as undernourished; whereas BMI identified a higher prevalence of obesity during the initial phases of treatment, which may reflect the limitations of BMI [5]. Although inaccuracies can arise from arm anthropometry, the intra- and inter-TEM of TSF and MUAC were minimal and unlikely to have contributed to these discrepancies. SF-BIA can be influenced by dramatic weight changes and hydration. Nonetheless, FFM% and FM% results from arm anthropometry and SF-BIA followed the same trajectories and revealed good limits of agreement. An alternative to SF-BIA is a multi-frequency BIA, which would address these limitations [11].

4.3. Factors contributing to changes in nutritional status (BMI centile) and associations between nutritional status and clinical outcome

Treatment risk was the most important factor contributing to changes in BMI during the first 3 months of treatment. High risk treatment protocols contributed to an increased risk of undernutrition, whereas low treatment risk protocols contributed to an increased in overnutrition. These findings have also been supported by others [18]. Importantly, TEI and diagnostic criteria contributed to changes in BMI when these were analysed independently.

Like others [52], undernutrition at diagnosis was significantly associated with an event and 14 times more likely to have an event than their well-nourished and overnourished counterparts. When severity of disease was also considered, most undernourished children were receiving high risk treatment protocols, suggesting that nutritional status is likely to be affected by both severity of disease and treatment risk and that children in high risk treatment protocols are more likely to be undernourished at diagnosis and to relapse, become palliative or to die. Undoubtedly, more research is warranted to confirm these findings.

Our findings have several clinical implications. Firstly, we highly recommend the monitoring of both growth and body composition by using either arm anthropometry or BIA. By adopting these measures, the excessive accumulation of fat in the adipose tissue could be identified earlier and dietary advice including TEI could be tailored accordingly. The muscle wasting would also be detected at an early stage. Whilst some degree of muscle wasting resulting from the initial acute phase response is inevitable [5], attempts should be made to minimise this at such critical stages. This could be achieved by increasing protein and introducing physical activity, especially when side-effects have improved [19]. Finally, in view of the vulnerability of children treated with high risk protocols, they should be targeted to prevent or reduce the risk of undernutrition during the initial 3 months; whilst careful matching of TER and TEI and close monitoring should be performed to prevent overfeeding. It is essential that easy to use and up to date National Growth Charts for arm anthropometry and body composition are developed for clinical implementation and training implemented to improve accuracy of measurements.

4.4. Limitations of the study and future research

The reduced sample size at later stages of the study precluded considering factors contributing to malnutrition beyond 18 months. The arm anthropometry reference ranges are based on date from many years ago; nonetheless, it is the only one that offers a full reference for children between the ages of 0–18 [10] and 1–18 years [9]. The assessment of physical activity by means of accelerometers proved too challenging for patients and their families. Future studies should use practical methods such as validated physical activity questionnaires, which are less accurate, but have proved more successful [19]. Future research should include high quality multicenter and international population based prospective cohort studies that are better able to identify patterns of change in different type of paediatric cancers and at later stages. In order to reduce the prevalence of malnutrition and to improve short and long-term outcomes, clinical guidelines specifically designed for nutritional screening, monitoring and management of paediatric cancer patients are urgently needed. Finally, high quality clinical trials should incorporate the effects of nutritional treatments and physical activity on the short and long term effects of nutritional status and clinical outcome.

5. Conclusions

In conclusion, our results highlight that children diagnosed and treated for cancer are at high risk of undernutrition and PEM, particularly during the initial 3 months of treatment, and overnutrition at later stages. The single most important factor contributing to undernutrition during the first 3 months of treatment was high treatment risk. Furthermore, no other clear factors assessed in this study contributed to malnutrition at later stages and undernutrition was associated with poorer clinical outcomes. Importantly, we recommend the use of arm anthropometry and BIA to all paediatric cancer patients during treatment at a minimum of 3 months intervals initially and every 6 months thereafter to prevent malnutrition.

Disclaimers

The authors have not disclaimers to declare and no conflict of interest.

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Author contributions

The following statements should be used: Conceptualization, RRI, IP, DW, MB, JMcK, ID; Methodology, RRI, IP, DW, JMcK; Software, NA.; Validation, DW; Formal Analysis, RRI and IP; Investigation, RRI and IP; Resources, MB, DW, JMcK; Data Curation, RRI, IP; Writing-Original Draft Preparation, RRI; Writing-Review & Editing, RRI, IP, DW, MB, JMcK and ID.; Visualization, IP, RRI and MB; Supervision, DW, JMcK and ID; Project Administration, DW, JMcK; Funding Acquisition, DW, MB, JMcK,

Conflicts of interest

The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, and in the decision to publish the results.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnesp.2019.04.006.

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